TAB 22

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

TRANSMITTED VIA FACSIMILE

February 1, 2001

Fred Hassan
President and CEO
Pharmacia Corporation
100 Route 206 North
Peapack, New Jersey 07977

RE: NDA 20-998
Celebrex (celecoxib) capsules
MACMIS ID # 8432

WARNING LETTER

Dear Mr. Hassan:

This Warning Letter concerns Pharmacia Corporation's (Pharmacia) promotional activities and materials for the marketing of Celebrex (celecoxib) capsules. Specifically, we refer to promotional audio conferences given on behalf of Pharmacia[1] by James McMillen, MD, and certain materials used to promote Celebrex. As part of its routine monitoring and surveillance program, the Division of Drug Marketing, Advertising, and Communications (DDMAC) has reviewed your promotional activities and materials and has concluded that they are false, lacking in fair balance, or otherwise misleading in violation of the Federal Food, Drug, and Cosmetic Act (the Act) and applicable regulations. See 21 U.S.C. §§ 331(a) and (b), 352(a), (f), and (n).

You have engaged in repeated promotional activities that minimize the potentially serious risk of using Celebrex and Coumadin (warfarin) concomitantly. Your minimization of this risk raises significant public health and safety concerns because it minimizes the risk of significant bleeding. Your promotional activities that minimize this risk are particularly troublesome because we have previously objected in two untitled letters to your promotional materials for Celebrex that, among other violations, minimized the Celebrex / Coumadin drug interaction. Based upon your assurances that corrective steps had been taken in order to prevent future violative promotional activities of this type, we considered these matters closed. Despite your assurances, however, your violative promotion of Celebrex has continued.

[1] Pharmacia & Upjohn merged with Monsanto Company (parent company of G.D. Searle & Co.) on April 3, 2000

Background

Since Celebrex's approval on December 31, 1998, post-marketing bleeding events have occurred in patients receiving Celebrex concurrently with warfarin. In fact, these post-marketing bleeding events ultimately led to the June 10, 1999, "Special Supplement—Changes Being Effected" labeling supplement. This supplement included a change in the Precautions Section of the approved product labeling (PI) for Celebrex to inform healthcare professionals about the need to monitor anticoagulant therapy closely when Celebrex and warfarin are used in combination. Specifically, the Precautions section of the PI for Celebrex includes risk information that states:

> [a]nticoagulant activity should be monitored, particularly in the first few days, after initiating or changing CELEBREX therapy in patients receiving warfarin or similar agents, since these patients are at an increased risk of bleeding complications. . . . in post-marketing experience, bleeding events have been reported, predominately in the elderly, in association with increases in prothrombin time in patients receiving CELEBREX concurrently with warfarin.

As a result of this important new risk information being added to the PI, we requested that you revise your promotional materials for Celebrex to include this new risk information. Specifically, our letter dated June 24, 1999, requested that promotional materials for Celebrex that include presentations about the use of Celebrex with warfarin, or drug interaction information in general, be revised to include prominent disclosure of the new risk information related to post-marketing bleeding events. We also informed you that your revised materials should alert healthcare providers about the need to monitor anticoagulant activity, particularly in the first few days, after initiating or changing Celebrex therapy in patients receiving warfarin. We requested that these revisions be completed no later than thirty days from the date of our letter.

In your letter dated July 23, 1999, you stated that revisions were made to your promotional materials for Celebrex, including the master sales aid. Furthermore, you stated that future professional journal advertisements for Celebrex would include the new risk information regarding the interaction between Celebrex and warfarin.

Promotional Audio Conferences

We have become aware of five promotional audio conferences presented on behalf of Pharmacia by Dr. James McMillen that are in violation of the Act and its implementing regulations. These audio conferences were held on March 7, 2000, March 23, 2000, May 2, 2000, May 4, 2000, and May 16, 2000.

On May 5, 2000, we sent you a written inquiry concerning your involvement with and influence on the initiation, preparation, development, and publication of audio conferences given by Dr. McMillen. We also asked you to describe the nature of the relationship between you and Dr. McMillen. In your response dated May 19, 2000, you stated:

> [o]ur company policy and operational basis is to require that our speakers follow the content of our approved slide kit, to not discuss off-label uses in their

> presentations, to adhere to the promotional regulations, and to provide disclosure of the funding of the program. We did have a report that Dr. McMillen was not adhering to all of our instructions, and in fact, brought him in to corporate headquarters in November, 1999, for retraining on these issues. Subsequent to our meeting with Dr. McMillen, we monitored his speeches and were reassured that he understood his obligations and was following our company policy.

Despite your assurances about retraining and monitoring of Dr. McMillen, subsequent programs by him on your behalf are false or misleading. Our specific objections follow.

Minimizing Celebrex / Coumadin Interaction

The statements made during promotional audio conferences identified above minimized the risk of Celebrex therapy in patients who are also taking Coumadin (warfarin). For example, in your March 23, 2000, audio conference you stated that there is no drug interaction between Celebrex and Coumadin. Specifically, you claimed that:

> Yes, Celebrex and Vioxx are different compounds. They have different reactions in the body. They are not interchangeable. Celebrex has shown drug interactions with lithium and Diflucan. Vioxx has not shown any drug interactions with lithium and Diflucan. Vioxx has shown drug interactions with Rifampin, Coumadin, and methotrexate. Celebrex, no drug interactions with those drugs.

Your direct statement that Celebrex does not interact with Coumadin directly contradicts the PI that clearly states, "...in post-marketing experience, bleeding events have been reported, predominately in the elderly, in association with increases in prothrombin time in patients receiving CELEBREX concurrently with warfarin." As previously stated, the PI for Celebrex was purposefully changed in response to these post-marketing bleeding events that have resulted from the concomitant use of Celebrex and Coumadin in order to warn of the very interaction that your promotion denied.

Your message that Celebrex does not interact with Coumadin is reinforced in the audio conferences by your selective presentation of Vioxx's (rofecoxib) labeling change regarding its risks in patients taking Coumadin. Your selective presentation of Vioxx's labeling change about its use with Coumadin, and failure to state that Celebrex's PI was also changed for the same reason, further implies that Celebrex and Coumadin can be used safely together with no risks. In addition, your failure to present Celebrex's labeling change suggests Celebrex is safer than Vioxx in patients taking Coumadin when such has not been demonstrated by substantial evidence. This misleading suggestion is further reinforced by your claim during the March 23, 2000, audio conference that, "Celebrex is the non-steroidal of choice if one is needed when a patient is on Coumadin."

We note that earlier in your promotional audio conferences before the discussion of Celebrex's drug interactions, you state, "Now after 16 million prescriptions were out there for Celebrex there has been a very rare increase in prothrombin time and bleed in the elderly. So prothrombin should be monitored...." However, your disclosure that "prothrombin should be monitored" does not adequately convey the extent to which anticoagulation monitoring is required after

initiating or changing Celebrex therapy in patients who are taking Coumadin. Additionally, this disclosure does not correct your misleading message that Celebrex and Coumadin have no drug interaction.

Minimizing Contraindication

Your promotional audio conferences minimize Celebrex's contraindication in patients who have demonstrated allergic-type reactions to sulfonamides. For example, you state that, "...many other drugs such as Diuril, Hydrodiuril, Hyzaar, Vasoretic are contraindicated in those allergic to sulfonamides," and "...if you have used these drugs without worrying about a sulfonamide reaction, then Celebrex can be no different." Your suggestion that Celebrex can be safely used in patients who are allergic to sulfonamides if they have not had allergic reactions to other drugs that are contraindicated in those allergic to sulfonamides is inconsistent with Celebrex's labeled contraindication that states, "CELEBREX should not be given to patients who have demonstrated allergic-type reactions to sulfonamides." Therefore, your promotional audio conferences are misleading because they undermine the risks of Celebrex therapy in patients who have demonstrated allergic-type reactions to sulfonamides and are inconsistent with the PI for Celebrex.

Omission of Important Risk Information

Your promotional audio conferences fail to present other serious and important risks associated with Celebrex therapy. For example, your promotional audio conferences fail to present Celebrex's contraindication in patients who have experienced asthma, urticaria, or allergic-type reactions after taking aspirin or other NSAIDs. You also fail to present the gastrointestinal (GI) warning for Celebrex about the possibility of serious GI toxicity such as bleeding, ulceration, or perforation. Moreover, you fail to present Celebrex's precautions in patients who have liver and kidney disease, patient populations in which Celebrex's use is not recommended such as late pregnancy, as well as Celebrex's most common adverse events.

Unsubstantiated Comparative Claims

You make several unsubstantiated comparative claims throughout your presentations. For example, you claim that Celebrex is safer, or has fewer side effects, than all available NSAIDs when used in patients that are on Coumadin. Specifically, in your March 23, 2000 audio conference, you claim that, "...Celebrex is the non-steroidal of choice if one is needed when a patient is on Coumadin." However, Celebrex has not been studied in head-to-head trials prospectively designed to assess its safety compared to other NSAIDs in patients who are taking Coumadin. Therefore, your superiority claim that Celebrex is " the non-steroidal of choice" when compared to the entire class of NSAIDs is misleading because such has not been demonstrated by substantial evidence.

In your audio conferences, you claim that, "...going from a dose of 100 mg of Celebrex a day to an increase of 8 times that dose to 800 mg a day, there was no increase in endoscopic ulcers, no increase in edema, no increase in blood pressure. This information becomes extremely important to all of us if you compare this to the Vioxx research data." Your suggestion that Celebrex is safer, or has fewer side effects than Vioxx is false or misleading because such conclusions have

not been demonstrated by substantial evidence. Celebrex has not been compared to Vioxx in trials prospectively designed to assess these endpoints.

Another example of your unsubstantiated comparative claims, is your claim that, "...in rheumatoid arthritic patients taking Celebrex at 200 mg twice a day, this was more efficacious than 1000 mg of Naprosyn in rheumatoid arthritics." The study that you cited to support this superiority claim actually concludes that Celebrex produced improvement in the signs and symptoms of RA comparable to the improvements produced by Naprosyn. Therefore, your claim of Celebrex's superior efficacy to Naprosyn is false or misleading.

Promotion of Unapproved New Use and Dosing Regimen

Your audio conferences are misleading because they suggest that Celebrex is safe and effective in the treatment of acute pain. For example, you discuss a 400 patient, 5 day post-orthopedic surgical pain study comparing Celebrex to hydrocodone plus acetaminophen. You state that the results of the surgical pain study were that, "...over the first eight hours 200 mg of Celebrex had a similar onset of action and efficacy to 10 mg of hydrocodone plus 1000 mg of acetaminophen single dose. Now over the next five days, the Celebrex was as effective as the narcotic with less drop-offs for lack of efficacy and less drop-offs for adverse events." Celebrex was not approved for an acute pain indication after review of six studies that were submitted to the Agency prior to Celebrex's approval. Additionally, [redacted] and were also deemed insufficient to support Celebrex's effectiveness for the treatment of acute pain. Therefore, your audio conferences promote an unapproved new use for Celebrex.

You also promote an unapproved dosing regimen for Celebrex. For example, you state, " In this [RA] study the dose of Celebrex could go up to 800 mg a day and this accomplished with no increase in adverse events. Yes, this was one of our hopes for COX-2 technology that you could double the dose a few times without increasing toxicity." The approved dosing regimen for Celebrex for RA however, is 100 to 200 mg twice daily. Therefore, your suggestion that Celebrex can be safely dosed at 800 mg per day (double the approved dose) promotes an unapproved dosing regimen and is misleading.

Violative Celebrex Promotional Labeling Pieces

We have identified a sales aid (CE18586Q), a four-sided card (CE18528W · YCE18528W), and a wall chart entitled, "Commonly Available Sulfur-Containing Drugs" (YCE18591W) that are false or misleading in violation of the Act for similar reasons as stated above.

Specifically, these materials minimize the importance of Celebrex's contraindication in patients who have demonstrated allergic-type reactions to sulfonamides. For example, they indicate that sulfonamides can generally be grouped into two categories, "antimicrobials" and "others." They further state that the antimicrobial sulfonamides have metabolites that may be more likely to cause primary allergic reactions than the metabolites of the "other" sulfonamide classes, thereby suggesting Celebrex is less likely to cause primary allergic reactions. However, your claims and representations that Celebrex is less likely to cause allergic reactions than other sulfur-containing compounds is inconsistent with Celebrex's labeled contraindications. Specifically, the PI states,

"Celebrex should not be given to patients who have demonstrated allergic-type reactions to sulfonamides." Therefore, your promotional materials are false or misleading because they suggest that Celebrex may be used safely in patients who have demonstrated allergic-type reactions to sulfonamides when, in fact, such is not the case.

Conclusions and Requested Actions

Your promotional activities described above raise significant health and safety concerns in that they minimize crucial risk information and promote Celebrex for unapproved new uses. In two previous untitled letters dated October 6, 1999, and April 6, 2000, we objected to your dissemination of promotional materials for Celebrex that misrepresented Celebrex's safety profile by minimizing the updated Celebrex / warfarin risk information and other risks, contained unsubstantiated comparative claims, and lacked fair balance. Based upon your written assurances that this violative promotion of Celebrex had been stopped, we considered these matters closed. Despite our prior written notification, and notwithstanding your assurances, Pharmacia has continued to engage in false or misleading promotion of Celebrex.

It is our understanding that you have decided to terminate this audio conference series with Dr. McMillen. Due to the seriousness of your violations and the fact that this behavior has continued despite your written assurances to the contrary, we request that you provide a detailed response to the issues raised in this Warning Letter on or before February 15, 2001. This response should contain an action plan that includes a comprehensive plan to disseminate corrective messages about the issues discussed in this letter to the audiences that received these misleading messages. This corrective action plan should also include:

1. Immediately ceasing the dissemination of all promotional activities and materials for Celebrex that contain violations like those outlined in this letter.

2. Issuing a "Dear Healthcare provider" letter to correct false or misleading impressions and information. This proposed letter should be submitted to us for review. After agreement is reached on the content and audience, the letter should be disseminated by direct mail to all healthcare providers who were, or may have been exposed to the violative promotion.

3. A written statement of your intent to comply with "1" and "2" above.

Your written response should be received no later than February 15, 2001. If you have any questions or comments, please contact the undersigned, Spencer Salis, Pharm. D., or Mark Askine R.Ph., by facsimile at (301) 594-6771, or at the Food and Drug Administration, Division of Drug Marketing, Advertising and Communications, HFD-42, Rm. 17B-20, 5600 Fishers Lane, Rockville, MD 20857. We remind you that only written communications are considered official.

In all future correspondence regarding this particular matter, please refer to MACMIS ID #8432 in addition to the NDA number.

The violations discussed in this letter do not necessarily constitute an exhaustive list. We are continuing to evaluate other aspects of your promotional campaign for Celebrex, and may

determine that additional remedial messages will be necessary to fully correct the false or misleading messages resulting from your violative conduct.

Failure to respond to this letter may result in regulatory action, including seizure or injunction, without further notice.

Sincerely,

/S/

Thomas W. Abrams, R.Ph., MBA
Director
Division of Drug Marketing,
Advertising and Communications

CELEBREX AND SULFONAMIDES

Sulfonamides

- Sulfonamides can generally be grouped into 2 categories, antimicrobials and "others," based on metabolic pathways.[1-4]
- The *antimicrobial* sulfonamides such as Bactrim™, Septra®, and Gantrisin® have metabolites that may be more likely to cause primary allergic reactions than the metabolites of the "other" sulfonamide classes such as diuretics, sulfonylureas, etc.[1-13]
- "Sulfa" is a popular term that is broadly used to refer to sulfur-containing antibiotics and is associated with antimicrobial sulfonamides.[14,15]
- CELEBREX is not an antimicrobial; it falls into the "other" group of sulfonamides.
- Many commonly prescribed medications are sulfonamides, including Lasix®, Hyzaar®, Ziac®, Imitrex®, and Glynase® PresTab®.[16]

Clinical Implications

- CELEBREX is contraindicated in patients who have *demonstrated* allergic-type reactions to sulfonamides.
- This contraindication is based on chemical structure.[17]
- Due to the presence of a sulfonamide moiety on the CELEBREX molecule, patients who had demonstrated allergic-type reactions to sulfonamides were proactively excluded from the CELEBREX clinical trials.[17]
- The overall rate of hypersensitivity to all sulfonamide-containing agents in the general population is low, estimated at approximately 3%.[4,9,18-20]
- 97% of the general population—the vast majority—are not allergic to sulfonamides.[4,9,18-20]
- Patients who have *not demonstrated* allergic-type reactions to sulfonamides are potential candidates for CELEBREX.

Contraindications—CELEBREX is contraindicated in patients with known hypersensitivity to celecoxib; in patients who have demonstrated allergic-type reactions to sulfonamides; and in patients who have experienced asthma, urticaria, or allergic-type reactions after taking aspirin or other NSAIDs.

Serious GI toxicity can occur with or without warning symptoms with NSAIDs.

In clinical trials, most common side effects of CELEBREX were dyspepsia, diarrhea, and abdominal pain, and were generally mild to moderate.

References: 1. Mandell GL, Petri WA Jr. Antimicrobial agents (continued): sulfonamides, trimethoprim-sulfamethoxazole, quinolones, and agents for urinary tract infections. In: Gilman AG, consulting ed; Hardman JG, Limbird LE, eds-in-chief; Molinoff PB, Roddon RW, eds. *Goodman & Gilman's The Pharmacological Basis of Therapeutics*. 9th ed. New York, NY: McGraw-Hill Book Co; 1996:1057-1062. 2. Montanaro A. Sulfonamide allergy. *Immunol Allergy Clin North Am*. 1998;18:843-850. 3. Cribb AE, Lee BL, Trepanier LA, Spielberg SP. Adverse reactions to sulphonamide and sulphonamide-trimethoprim antimicrobials: clinical syndromes and pathogenesis. *Adverse Drug React Toxicol Rev*. 1996;15:9-50. 4. Duncan C. Sulfonamide cross-allergenicity—answers to common questions. *Hosp Pharm*. 1989;24:666-668. 5. Sullivan TJ. Cross-reactions among furosemide, hydrochlorothiazide, and sulfonamides. *JAMA*. 1991;265:120-121. 6. Rieder MJ, Uetrecht J, Shear NH, Cannon M, Miller M, Spielberg SP. Diagnosis of sulfonamide hypersensitivity reactions by in-vitro "rechallenge" with hydroxylamine metabolites. *Ann Intern Med*. 1989;110:286-289. 7. Weinstein L, Madoff MA, Samet CM. The sulfonamides. *N Engl J Med*. 1960;265(16):793-800. *(Continued on back.)*

CELEBREX™
(CELECOXIB CAPSULES) 100 mg 200 mg

Please see full prescribing information inside.

PRESCRIBE WITH CONFIDENCE

Commonly used* sulfonamide-containing drugs

Many commonly prescribed medications are sulfonamides, including Lasix, Hyzaar, Ziac, Imitrex, Glynase Pres Tab, Bactrim, Septra, and Gantrisin.

Non-antimicrobials with sulfonamide-related contraindications

Brand	Drug(s)	Drug class of agent containing sulfonamide group	Company	Sulfonamide-related contraindication[2,21]
Capozide®	captopril/ hydrochlorothiazide*	Angiotensin-I inhibitor/ diuretic	Bristol-Myers Squibb Company	previously demonstrated hypersensitivity to...other sulfonamide derived drugs[22]
[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
Diuril®	chlorothiazide	Diuretic	Merck & Co., Inc.	Hypersensitivity to...other sulfonamide-derived drugs[16]
[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
HydroDiuril®	hydrochlorothiazide	Diuretic	Merck & Co., Inc.	Hypersensitivity to...other sulfonamide-derived drugs[16]
[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
Lozol®	indapamide	Antihypertensive/ diuretic	Rhône-Poulenc Rorer Pharmaceuticals Inc.	...hypersensitivity...to other sulfonamide-derived drugs[22]
[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
Tenoretic®	atenolol/ chlorthalidone*	Beta-blocker/ diuretic	Zeneca Pharmaceuticals	...hypersensitivity to... sulfonamide-derived drugs[16]
[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
Zestoretic®	lisinopril/ hydrochlorothiazide*	Angiotensin-I inhibitor/ diuretic	Zeneca Pharmaceuticals	...hypersensitivity to other sulfonamide-derived drugs[16]
Ziac®	bisoprolol/ hydrochlorothiazide*	Beta-blocker/ diuretic	Lederle Laboratories	...hypersensitivity to other sulfonamide-derived drugs[16]

* Sulfonamide-containing component.

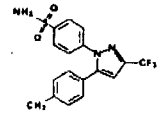
References, continued: 8. Weinstein L, Madoff MA, Samet CM. The sulfonamides (continued). *N Engl J Med.* 1960;265(17):842-849. 9. Weinstein L, Madoff MA, Samet CM. The sulfonamides (concluded). *N Engl J Med.* 1960;265(19):952-957. 10. Merk HF, Baron J, Kawakubo Y, Hertl M, Jugert F. Metabolites and allergic reactions. *Clin Exp Allergy.* 1998;28(suppl 4):21-24. 11. Shear NH, Spielberg SP, Grant DM, Tang BK, Kalow W. Differences in metabolism of sulfonamides predisposing to idiosyncratic toxicity. *Ann Intern Med.* 1986;105:179-184. 12. Nakamura H, Uetrecht J, Cribb AE, et al. *In vitro* formation, disposition and toxicity of N-acetoxy-sulfamethoxazole, a potential mediator of sulfamethoxazole toxicity. *J Pharmacol Exp Ther.* 1995;274:1099-1104. 13. Weisbecker CA, Fraunfelder FT, Gold AA, Naidoff M, Tippermann R, ed consultants and contributors. *Physicians' Desk Reference for Ophthalmology.* 23rd ed. Montvale, NJ: Medical Economics Co; 1995. 14. Silverman HM, ed-in-chief. *The Pill Book.* 6th ed. New York, NY: Bantam Books; 1994. 15. Sonnedecker G. *Kremers and Urdang's History of Pharmacy.* 4th ed (reprint). Madison, Wis: American Institute of the History of Pharmacy; 1986. 16. Arky R, med consultant; Greenberg SB, VP Directory Services. *Physicians' Desk Reference.* 53rd ed. Montvale, NJ: Medical Economics Co; 1999. 17. Data on file, GD Searle & Co (Patterson R, LaCombe M, Bello A, Lefkowich J). Safety profile of celecoxib in sulfonamide-hypersensitive patients. Submitted to *Fam Med.* 18. Gruchalla RS, Pesenko RD, Do TT, Skiest DJ. Sulfonamide-induced reactions in desensitized patients with AIDS—the role of covalent protein haptenation by sulfamethoxazole. *J Allergy Clin Immunol.* 1998;101:371-378. 19. Kucera CM, Greenberger PA. Adverse drug reactions: treatment and prevention. *Hosp Med.* 1996 (Dec):11-24. 20. Walley T, Coleman JW. Allergic drug reactions: incidence and avoidance. *Clin Immunother.* 1994;1:101-109. 21. IMS America, National Prescription Audit, January 1993–June 1999. 22. Denniston PL Jr, ed. *1994 Physicians GenR$_x$.* Smithtown, NY: Physicians GenR$_x$; 1994:II-324–II-325, II-1200, II-1201.

SEARLE Pfizer

CELEBREX™
(celecoxib capsules)

DESCRIPTION

CELEBREX (celecoxib) is chemically designated as 4-[5-(4-methylphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl] benzenesulfonamide and is a diaryl substituted pyrazole. It has the following chemical structure:



The empirical formula for celecoxib is $C_{17}H_{14}F_3N_3O_2S$, and the molecular weight is 381.38.

CELEBREX oral capsules contain 100 mg and 200 mg of celecoxib.

The inactive ingredients in CELEBREX capsules include: croscarmellose sodium, edible inks, gelatin, lactose monohydrate, magnesium stearate, povidone, sodium lauryl sulfate and titanium dioxide.

CLINICAL PHARMACOLOGY

Mechanism of Action: CELEBREX is a nonsteroidal anti-inflammatory drug that exhibits anti-inflammatory, analgesic, and antipyretic activities in animal models. The mechanism of action of CELEBREX is believed to be due to inhibition of prostaglandin synthesis, primarily via inhibition of cyclooxygenase-2 (COX-2), and at therapeutic concentrations in humans, CELEBREX does not inhibit the cyclooxygenase-1 (COX-1) isoenzyme.

Pharmacokinetics:

Absorption

Peak plasma levels of celecoxib occur approximately 3 hrs after an oral dose. Both peak plasma levels (C_{max}) and area under the curve (AUC) are roughly dose proportional across the clinical dose range of 100–200 mg studied. At higher doses, under fasting conditions, there is a less than proportional increase in C_{max} and AUC which is thought to be due to the low solubility of the drug in aqueous media. Because of the low solubility, absolute bioavailability studies have not been conducted. With multiple dosing, steady state conditions are reached on or before day 5.

The pharmacokinetic parameters of celecoxib in a group of healthy subjects are shown in Table 1.

Table 1
Summary of Single Dose (200 mg) Disposition Kinetics of Celecoxib in Healthy Subjects[1]
Mean (%CV) PK Parameter Values

C_{max}, ng/mL	T_{max}, hr	Effective $t_{1/2}$, hr	V_{ss}/F, L	CL/F, L/hr
705 (38)	2.8 (37)	11.2 (31)	429 (34)	27.7 (28)

[1] Subjects under fasting conditions (n=36, 18–52 yrs.)

Food Effects

When CELEBREX capsules were taken with a high fat meal, peak plasma levels were delayed for about 1 to 2 hours with an increase in total absorption (AUC) of 10% to 20%. Coadministration of CELEBREX with an aluminum- and magnesium-containing antacid resulted in a reduction in plasma celecoxib concentrations with a decrease of 37% in C_{max} and 10% in AUC. CELEBREX capsules can be administered without regard to the timing of meals.

Distribution

In healthy subjects, celecoxib is highly protein bound (~97%) within the clinical dose range. *In vitro* studies indicate that celecoxib binds primarily to albumin and, to a lesser extent, α_1-acid glycoprotein. The apparent volume of distribution at steady state (V_{ss}/F) is approximately 400 L, suggesting extensive distribution into the tissues. Celecoxib is not preferentially bound to red blood cells.

Metabolism

Celecoxib metabolism is primarily mediated via cytochrome P450 2C9. Three metabolites, a primary alcohol, the corresponding carboxylic acid and its glucuronide conjugate, have been identified in human plasma. These metabolites are inactive as COX-1 or COX-2 inhibitors. Patients who are known or suspected to be P450 2C9 poor metabolizers based on a previous history should be administered celecoxib with caution as they may have abnormally high plasma levels due to reduced metabolic clearance.

Excretion

Celecoxib is eliminated predominantly by hepatic metabolism with little (<3%) unchanged drug recovered in the urine and feces. Following a single oral dose of radiolabeled drug, approximately 57% of the dose was excreted in the feces and 27% was excreted into the urine. The primary metabolite in both urine and feces was the carboxylic acid metabolite (73% of dose) with low amounts of the glucuronide also appearing in the urine. It appears that the low solubility of the drug prolongs the absorption process making terminal half-life ($t_{1/2}$) determinations more variable. The effective half-life is approximately 11 hours under fasted conditions. The apparent plasma clearance (CL/F) is about 500 mL/min.

Special Populations

Geriatric: At steady state, elderly subjects (over 65 years old) had a 40% higher C_{max} and a 50% higher AUC compared to the young subjects. In elderly females, celecoxib C_{max} and AUC are higher than those for elderly males, but these increases are predominantly due to lower body weight in elderly females. Dose adjustment in the elderly is not generally necessary. However, for patients of less than 50 kg in body weight, initiate therapy at the lowest recommended dose.

Pediatric: CELEBREX capsules have not been investigated in pediatric patients below 18 years of age.

Race: Meta-analysis of pharmacokinetic studies has suggested an approximately 40% higher AUC of celecoxib in Blacks compared to Caucasians. The cause and clinical significance of this finding is unknown.

Hepatic Insufficiency: A pharmacokinetic study in subjects with mild (Child-Pugh Class I) and moderate (Child-Pugh Class II) hepatic impairment has shown that steady-state celecoxib AUC is increased about 40% and 180%, respectively, above that seen in healthy control subjects. Therefore, CELEBREX capsules should be introduced at a reduced dose in patients with moderate hepatic impairment. Patients with severe hepatic impairment have not been studied. The use of CELEBREX in patients with severe hepatic impairment is not recommended.

Renal Insufficiency: In a cross-study comparison, celecoxib AUC was approximately 40% lower in patients with chronic renal insufficiency (GFR 35–60 mL/min) than that seen in subjects with normal renal function. No significant relationship was found between GFR and celecoxib clearance. Patients with severe renal insufficiency have not been studied.

Drug Interactions

Also see PRECAUTIONS—Drug Interactions.

General: Significant interactions may occur when celecoxib is administered together with drugs that inhibit P450 2C9. *In vitro* studies indicate that celecoxib is not an inhibitor of cytochrome P450 2C9, 2C19 or 3A4.

Clinical studies with celecoxib have identified potentially significant interactions with fluconazole and lithium. Experience with nonsteroidal anti-inflammatory drugs (NSAIDs) suggests the potential for interactions with furosemide and ACE inhibitors. The effects of celecoxib on the pharmacokinetics and/or pharmacodynamics of glyburide, ketoconazole, methotrexate, phenytoin, and tolbutamide have been studied *in vivo* and clinically important interactions have not been found.

CLINICAL STUDIES

Osteoarthritis (OA): CELEBREX has demonstrated significant reduction in joint pain compared to placebo. CELEBREX was evaluated for treatment of the signs and the symptoms of OA of the knee and hip in approximately 4,200 patients in placebo- and active-controlled clinical trials of up to 12 weeks duration. In patients with OA, treatment with CELEBREX 100 mg BID or 200 mg QD resulted in improvement in WOMAC (Western Ontario and McMaster Universities) osteoarthritis index, a composite of pain, stiffness, and functional measures in OA. In three 12-week studies of pain accompanying OA flare, CELEBREX doses of 100 mg BID and 200 mg BID provided significant reduction of pain within 24–48 hours of initiation of dosing. At doses of 100 mg BID or 200 mg BID the effectiveness of CELEBREX was shown to be similar to that of naproxen 500 mg BID. Doses of 200 mg BID provided no additional benefit above that seen with 100 mg BID. A total daily dose of 200 mg has been shown to be equally effective whether administered as 100 mg BID or 200 mg QD.

Rheumatoid Arthritis (RA): CELEBREX has demonstrated significant reduction in joint tenderness/pain and joint swelling compared to placebo. CELEBREX was evaluated for treatment of the signs and symptoms of RA in approximately 2,100 patients in placebo- and active-controlled clinical trials of up to 24 weeks in duration. CELEBREX was shown to be superior to placebo in these studies, using the ACR20 Responder Index, a composite of clinical, laboratory, and functional measures in RA. CELEBREX doses of 100 mg BID and 200 mg BID were similar in effectiveness and both were comparable to naproxen 500 mg BID.

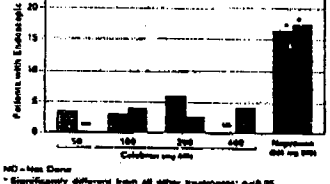
Although CELEBREX 100 mg BID and 200 mg BID provided similar overall effectiveness, some patients derived additional benefit from the 200 mg BID dose. Doses of 400 mg BID provided no additional benefit above that seen with 100–200 mg BID.

Special Studies

Gastrointestinal: Scheduled upper GI endoscopic evaluations were performed in over 4,500 arthritis patients who were enrolled in five controlled randomized 12–24 week trials using active comparators, two of which also included placebo controls. Twelve-week endoscopic ulcer data are available on approximately 1,400 patients and 24 week endoscopic ulcer data are available on 184 patients on CELEBREX at doses ranging from 50–400 mg BID. In all three studies that included naproxen 500 mg BID, and in the study that included ibuprofen 800 mg TID, CELEBREX was associated with a statistically significantly lower incidence of endoscopic ulcers over the study period. Two studies compared CELEBREX with diclofenac 75 mg BID; one study revealed a statistically significantly higher prevalence of endoscopic ulcers in the diclofenac group at the study endpoint (6 months on treatment), and one study revealed no statistically significant difference between cumulative endoscopic ulcer incidence rates in the diclofenac and CELEBREX groups after 1, 2, and 3 months of treatment. There was no consistent relationship between the incidence of gastroduodenal ulcers and the dose of CELEBREX over the range studied.

Figure 1 and Table 2 summarize the incidence of endoscopic ulcers in two 12-week studies that enrolled patients in whom baseline endoscopies revealed no ulcers.

Figure 1
Incidence of Endoscopically Observed Gastroduodenal Ulcers after 12 Weeks of Treatment



NID = Not Done

* Significantly different from all other treatments; p≤0.05.

Celebrex 100 mg BID and 200 mg QD, BID are the recommended doses.

These studies were not powered to compare the endoscopic ulcer rates of Celebrex vs. placebo.

Study 1: placebo ulcer rate = 3.3%

Study 2: placebo ulcer rate = 2.6%

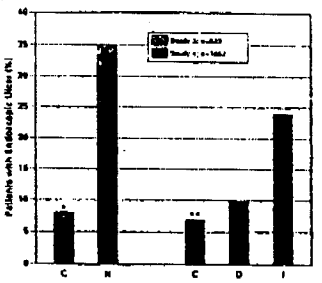
Table 2
Incidence of Gastroduodenal Ulcers from Endoscopic Studies in OA and RA Patients

	3 Month Studies	
	Study 1 (n=1149)	Study 2 (n=1043)
Placebo	2.3% (5/217)	2.0% (4/200)
Celebrex 50 mg BID	3.4% (8/233)	—
Celebrex 100 mg BID	3.1% (7/227)	4.0% (9/223)
Celebrex 200 mg BID	5.9% (13/221)	2.7% (6/219)
Celebrex 400 mg BID	—	4.1% (8/197)
Naproxen 500 mg BID	16.2% (34/210)*	17.6% (37/210)*

* p≤0.05 vs all other treatments

Figure 2 and Table 3 summarize data from two 12-week studies that enrolled patients in whom baseline endoscopies revealed no ulcers. Patients underwent interval endoscopies every 4 weeks to give information on ulcer risk over time.

Figure 2
Cumulative Incidence of Gastroduodenal Ulcers Based on 4 Serial Endoscopies over 12 Weeks



* p<0.001 vs naproxen ** p<0.001 vs ibuprofen

C = Celecoxib 200 mg BID D = Diclofenac 75 mg BID
N = Naproxen 500 mg BID I = Ibuprofen 800 mg TID

Table 3
Incidence of Gastroduodenal Ulcers from 3-Month Serial Endoscopy Studies in OA and RA Patients

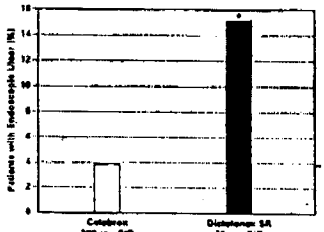
	Week 4	Week 8	Week 12	Final
Study 3 (n=1052)				
Celebrex 200 mg BID	4.8% (19/252)*	2.2% (5/227)*	1.5% (3/196)*	7.5% (20/266)*
Naproxen 500 mg BID	19.0% (47/247)	14.2% (26/182)	9.9% (14/141)	34.6% (88/257)
Study 4 (n=1052)				
Celebrex 200 mg BID	2.8% (13/337)†	2.4% (7/293)†	1.8% (5/274)†	7.6% (25/326)†
Diclofenac 75 mg BID	6.1% (19/350)	3.3% (10/305)	2.9% (8/278)	9.7% (36/372)
Ibuprofen 800 mg TID	13.0% (42/323)	8.2% (19/241)	9.6% (21/218)	23.3% (78/334)

* p≤0.05 Celebrex vs. naproxen based on interval and cumulative endpoints

† p≤0.05 Celebrex vs. ibuprofen based on interval and cumulative endpoints

One randomized and double-blinded 6-month study in 430 RA patients was conducted in which an endoscopic examination was performed at 6 months. The results are shown in Figure 3.

Figure 3
Prevalence of Endoscopically Observed Gastroduodenal Ulcers after Six Months of Treatment in Patients with Rheumatoid Arthritis



* Significantly different from Celebrex; p<0.001

The correlation between findings of endoscopic studies, and the relative incidence of clinically serious upper GI events that may be observed with different products, has not been fully established. Serious clinically significant upper GI bleeding has been observed in patients receiving CELEBREX in controlled and open-labeled trials, albeit infrequently (see WARNINGS – Gastrointestinal (GI) effects). Prospective, long-term studies required to compare the incidence of serious, clinically significant upper GI adverse events in patients taking CELEBREX vs. comparator NSAID products have not been performed.

Use with Aspirin: Approximately 11% of patients (440/4,000) enrolled in 4 of the 5 endoscopic studies were taking aspirin (≤325 mg/day). In the CELEBREX groups, the endoscopic ulcer rate appeared to be higher in aspirin users than in non-users. However, the increased rate of ulcers in these aspirin users was less than the endoscopic ulcer rates observed in the active comparator groups, with or without aspirin.

Platelets: In clinical trials, CELEBREX at single doses up to 800 mg and multiple doses of 600 mg BID for up to 7 days; duration (higher than recommended therapeutic doses) had no effect on platelet aggregation and bleeding time. Comparators (naproxen 500 mg BID, ibuprofen 800 mg TID, diclofenac 75 mg BID) significantly reduced platelet aggregation and prolonged bleeding time.

INDICATIONS AND USAGE

CELEBREX is indicated:

1) For relief of the signs and symptoms of osteoarthritis.
2) For relief of the signs and symptoms of rheumatoid arthritis in adults.

CONTRAINDICATIONS

CELEBREX is contraindicated in patients with known hypersensitivity to celecoxib.

CELEBREX should not be given to patients who have demonstrated allergic-type reactions to sulfonamides.

CELEBREX should not be given to patients who have experienced asthma, urticaria, or allergic-type reactions after taking aspirin or other NSAIDs. Severe, rarely fatal, anaphylactic-like reactions to NSAIDs have been reported in such patients (see WARNINGS—Anaphylactoid Reactions, and PRECAUTIONS—Preexisting Asthma).

WARNINGS

Gastrointestinal (GI) Effects—Risk of GI Ulceration, Bleeding, and Perforation

Serious gastrointestinal toxicity such as bleeding, ulceration, and perforation of the stomach, small intestine or large intestine, can occur at any time, with or without warning symptoms, in patients treated with nonsteroidal anti-inflammatory drugs (NSAIDs). Minor upper gastrointestinal problems, such as dyspepsia, are common and may also occur at any time during NSAID therapy. Therefore, physicians and patients should remain alert for ulceration and bleeding, even in the absence of previous GI tract symptoms. Patients should be informed about the signs and/or symptoms of serious GI toxicity and the steps to take if they occur. The utility of periodic laboratory monitoring has not been demonstrated, nor has it been adequately assessed. Only one in five patients who develop a serious upper GI adverse event on NSAID therapy is symptomatic. It has been demonstrated that upper GI ulcers, gross bleeding or perforation, caused by NSAIDs, appear to occur in approximately 1% of patients treated for 3–6 months, and in about 2–4% of patients treated for one year. These trends continue thus, increasing the likelihood of developing a serious GI event at some time during the course of therapy. However, even short-term therapy is not without risk.

It is unclear, at the present time, how the above rates apply to CELEBREX (see CLINICAL STUDIES – Special Studies). Among 5,285 patients who received CELEBREX in controlled clinical trials of 1 to 6 months duration (most were 3 month studies) at a daily dose of 200 mg or more, 2 (0.04%) experienced significant upper GI bleeding, at 14 and 22 days after initiation of dosing. Approximately 40% of these 5,285 patients were in studies that required them to be free of ulcers by endoscopy at study entry. Thus it is unclear if this study population is representative of the general population. Prospective, long-term studies required to compare the incidence of serious, clinically significant upper GI adverse events in patients taking CELEBREX vs. comparator NSAID products have not been performed.

NSAIDs should be prescribed with extreme caution in patients with a prior history of ulcer disease or gastrointestinal bleeding. Most spontaneous reports of fatal GI events are in elderly or debilitated patients and therefore special care should be taken in treating this population. To minimize the potential risk for an adverse GI event, the lowest effective dose should be used for the shortest possible duration. For high risk patients, alternate therapies that do not involve NSAIDs should be considered.

Studies have shown that patients with a *prior history of peptic ulcer disease and/or gastrointestinal bleeding* and who use NSAIDs, have a greater than 10-fold higher risk for developing a GI bleed than patients with neither of these risk factors. In addition to a past history of ulcer disease, pharmacoepidemiological studies have identified several other co-therapies or co-morbid conditions that may increase the risk for GI bleeding such as: treatment with oral corticosteroids, treatment with anticoagulants, longer duration of NSAID therapy, smoking, alcoholism, older age, and poor general health status.

Anaphylactoid Reactions

As with NSAIDs in general, anaphylactoid reactions may occur in patients without known prior exposure to CELEBREX. In post-marketing experience, very rare cases of anaphylactic reactions and angioedema have been reported in patients receiving CELEBREX. CELEBREX should not be given to patients with the aspirin triad. This symptom complex typically occurs in asthmatic patients who experience rhinitis with or without nasal polyps, or who exhibit severe, potentially fatal bronchospasm after taking aspirin or other NSAIDs (see CONTRAINDICATIONS and PRECAUTIONS—Preexisting Asthma). Emergency help should be sought in cases where an anaphylactoid reaction occurs.

Advanced Renal Disease

No information is available regarding the use of CELEBREX in patients with advanced kidney disease. Therefore, treatment with CELEBREX is not recommended in these patients. If CELEBREX therapy must be initiated, close monitoring of the patient's kidney function is advisable (see PRECAUTIONS—Renal Effects).

Pregnancy

In late pregnancy CELEBREX should be avoided because it may cause premature closure of the ductus arteriosus.

PRECAUTIONS

General: CELEBREX cannot be expected to substitute for corticosteroids or to treat corticosteroid insufficiency. Abrupt discontinuation of corticosteroids may lead to exacerbation of corticosteroid-responsive illness. Patients on prolonged corticosteroid therapy should have their therapy tapered slowly if a decision is made to discontinue corticosteroids.

The pharmacological activity of CELEBREX in reducing inflammation, and possibly fever, may diminish the utility of these diagnostic signs in detecting infectious complications of presumed noninfectious, painful conditions.

Hepatic Effects: Borderline elevations of one or more liver tests may occur in up to 15% of patients taking NSAIDs, and notable elevations of ALT or AST (approximately three or more times the upper limit of normal) have been reported in approximately 1% of patients in clinical trials with NSAIDs. These laboratory abnormalities may progress, may remain unchanged, or may be

with continuing therapy. Rare cases of severe reactions, including jaundice and fatal fulminant hepatitis, liver necrosis and hepatic failure (some with fatal outcome) have been reported with NSAIDs. In controlled clinical trials of CELEBREX, the incidence of borderline elevations of liver tests was 6% for CELEBREX and 5% for placebo, and approximately 0.2% of patients taking CELEBREX and 0.3% of patients taking placebo had notable elevations of ALT and AST.

A patient with symptoms and/or signs suggesting liver dysfunction, or in whom an abnormal liver test has occurred, should be monitored carefully for evidence of the development of a more severe hepatic reaction while on therapy with CELEBREX. If clinical signs and symptoms consistent with liver disease develop, or if systemic manifestations occur (e.g., eosinophilia, rash, etc.), CELEBREX should be discontinued.

Renal Effects: Long-term administration of NSAIDs has resulted in renal papillary necrosis and other renal injury. Renal toxicity has also been seen in patients in whom renal prostaglandins have a compensatory role in the maintenance of renal perfusion. In these patients, administration of a nonsteroidal anti-inflammatory drug may cause a dose-dependent reduction in prostaglandin formation and, secondarily, in renal blood flow, which may precipitate overt renal decompensation. Patients at greatest risk of this reaction are those with impaired renal function, heart failure, liver dysfunction, those taking diuretics and ACE inhibitors, and the elderly. Discontinuation of NSAID therapy is usually followed by recovery to the pretreatment state. Clinical trials with CELEBREX have shown renal effects similar to those observed with comparator NSAIDs.

Caution should be used when initiating treatment with CELEBREX in patients with considerable dehydration. It is advisable to rehydrate patients first and then start therapy with CELEBREX. Caution is also recommended in patients with pre-existing kidney disease (see WARNINGS – Advanced Renal Disease).

Hematological Effects: Anemia is sometimes seen in patients receiving CELEBREX. In controlled clinical trials the incidence of anemia was 0.8% with CELEBREX and 0.4% with placebo. Patients on long-term treatment with CELEBREX should have their hemoglobin or hematocrit checked if they exhibit any signs or symptoms of anemia or blood loss. CELEBREX does not generally affect platelet counts, prothrombin time (PT), or partial thromboplastin time (PTT), and does not appear to inhibit platelet aggregation at indicated dosages (See CLINICAL STUDIES—Special Studies—Platelets).

Fluid Retention and Edema: Fluid retention and edema have been observed in some patients taking CELEBREX (see ADVERSE REACTIONS). Therefore, CELEBREX should be used with caution in patients with fluid retention, hypertension, or heart failure.

Preexisting Asthma: Patients with asthma may have aspirin-sensitive asthma. The use of aspirin in patients with aspirin-sensitive asthma has been associated with severe bronchospasm which can be fatal. Since cross reactivity, including bronchospasm, between aspirin and other nonsteroidal anti-inflammatory drugs has been reported in such aspirin-sensitive patients, CELEBREX should not be administered to patients with this form of aspirin sensitivity and should be used with caution in patients with preexisting asthma.

Information for Patients: CELEBREX can cause discomfort and, rarely, more serious side effects, such as gastrointestinal bleeding, which may result in hospitalization and even fatal outcomes. Although serious GI tract ulcerations and bleeding can occur without warning symptoms, patients should be alert for the signs and symptoms of ulcerations and bleeding, and should ask for medical advice when observing any indicative signs or symptoms. Patients should be apprised of the importance of this follow-up (see WARNINGS—Risk of Gastrointestinal Ulceration, Bleeding and Perforation).

Patients should promptly report signs or symptoms of gastrointestinal ulceration or bleeding, skin rash, unexplained weight gain, or edema to their physicians.

Patients should be informed of the warning signs and symptoms of hepatotoxicity (e.g., nausea, fatigue, lethargy, pruritus, jaundice, right upper quadrant tenderness, and "flu-like" symptoms). If these occur, patients should be instructed to stop therapy and seek immediate medical therapy.

Patients should also be instructed to seek immediate emergency help in the case of an anaphylactoid reaction (see WARNINGS).

In late pregnancy CELEBREX should be avoided because it may cause premature closure of the ductus arteriosus.

Laboratory Tests: Because serious GI tract ulcerations and bleeding can occur without warning symptoms, physicians should monitor for signs or symptoms of GI bleeding.

During the controlled clinical trials, there was an increased incidence of hyperchloremia in patients receiving celecoxib compared with patients on placebo. Other laboratory abnormalities that occurred more frequently in the patients receiving celecoxib included hypophosphatemia, and elevated BUN. These laboratory abnormalities were also seen in patients who received comparator NSAIDs in these studies. The clinical significance of these abnormalities has not been established.

Drug Interactions

General: Celecoxib metabolism is predominantly mediated via cytochrome P450 2C9 in the liver. Co-administration of celecoxib with drugs that are known to inhibit 2C9 should be done with caution.

In vitro studies indicate that celecoxib, although not a substrate, is an inhibitor of cytochrome P450 2D6. Therefore, there is a potential for an *in vivo* drug interaction with drugs that are metabolized by P450 2D6.

ACE-inhibitors: Reports suggest that NSAIDs may diminish the antihypertensive effect of Angiotensin Converting Enzyme (ACE) inhibitors. This interaction should be given consideration in patients taking CELEBREX concomitantly with ACE-inhibitors.

Furosemide: Clinical studies, as well as post marketing observations, have shown that NSAIDs can reduce the natriuretic effect of furosemide and thiazides in some patients. This response has been attributed to inhibition of renal prostaglandin synthesis.

Aspirin: CELEBREX can be used with low dose aspirin. However, concomitant administration of aspirin with CELEBREX may result in an increased rate of GI ulceration or other complications, compared to use of CELEBREX alone (see CLINICAL STUDIES—Special Studies—Gastrointestinal). Because of its lack of platelet effects, CELEBREX is not a substitute for aspirin for cardiovascular prophylaxis.

Fluconazole: Concomitant administration of fluconazole at 200 mg QD resulted in a two-fold increase in celecoxib plasma concentration. This increase is due to the inhibition of celecoxib metabolism via P450 2C9 by fluconazole (see Pharmacokinetics—Metabolism). CELEBREX should be introduced at the lowest recommended dose in patients receiving fluconazole.

Lithium: In a study conducted in healthy subjects, mean steady-state lithium plasma levels increased approximately 17% in subjects receiving lithium 450 mg BID with CELEBREX 200 mg BID as compared to subjects receiving lithium alone. Patients on lithium treatment should be closely monitored when CELEBREX is introduced or withdrawn.

Methotrexate: In an interaction study of rheumatoid arthritis patients taking methotrexate, CELEBREX did not have a significant effect on the pharmacokinetics of methotrexate.

Warfarin: Anticoagulant activity should be monitored, particularly in the first few days, after initiating or changing CELEBREX therapy in patients receiving warfarin or similar agents, since these patients are at an increased risk of bleeding complications. The effect of celecoxib on the anticoagulant effect of warfarin was studied in a group of healthy subjects receiving daily doses of 2 to 5 mg of warfarin. In these subjects, celecoxib did not alter the anticoagulant effect of warfarin as determined by prothrombin time. However, in post-marketing experience, bleeding events have been reported, predominantly in the elderly, in association with increases in prothrombin time in patients receiving CELEBREX concurrently with warfarin.

Carcinogenesis, mutagenesis, impairment of fertility: Celecoxib was not carcinogenic in rats given oral doses up to 200 mg/kg for males and 10 mg/kg for females (approximately 2- to 4-fold the human exposure as measured by the AUC_{0-24} at 200 mg BID) or in mice given oral doses up to 25 mg/kg for males and 50 mg/kg for females (approximately equal to human exposure as measured by the AUC_{0-24} at 200 mg BID) for two years.

Celecoxib was not mutagenic in an Ames test and a mutation assay in Chinese hamster ovary (CHO) cells, nor clastogenic in a chromosome aberration assay in CHO cells and an *in vivo* micronucleus test in rat bone marrow.

Celecoxib did not impair male and female fertility in rats at oral doses up to 600 mg/kg/day (approximately 11-fold human exposure at 200 mg BID based on the AUC_{0-24}).

Pregnancy

Teratogenic effects: Pregnancy Category C. Celecoxib was not teratogenic in rabbits up to an oral dose of 60 mg/kg/day (equal to human exposure at 200 mg BID as measured by AUC_{0-24}); however, at oral doses ≥150 mg/kg/day (approximately 2-fold human exposure at 200 mg BID as measured by AUC_{0-24}), an increased incidence of fetal alterations, such as ribs fused, sternebrae fused and sternebrae misshapen, was observed. A dose-dependent increase in diaphragmatic hernias was observed in one of two rat studies at oral doses ≥30 mg/kg/day (approximately 6-fold human exposure based on the AUC_{0-24} at 200 mg BID). There are no studies in pregnant women. CELEBREX should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nonteretogenic effects: Celecoxib produced pre-implantation and post-implantation losses and reduced embryo/fetal survival in rats at oral dosages ≥50 mg/kg/day (approximately 6-fold human exposure based on the AUC_{0-24} at 200 mg BID). These changes are expected with inhibition of prostaglandin synthesis and are not the result of permanent alteration of female reproductive function, nor are they expected at clinical exposures. No studies have been conducted to evaluate the effect of celecoxib on the closure of the ductus arteriosus in humans. Therefore, use of CELEBREX during the third trimester of pregnancy should be avoided.

Labor and delivery: Celecoxib produced no evidence of delayed labor or parturition at oral doses up to 100 mg/kg in rats (approximately 7-fold human exposure as measured by the AUC_{0-24} at 200 mg BID). The effects of CELEBREX on labor and delivery in pregnant women are unknown.

Nursing mothers: Celecoxib is excreted in the milk of lactating rats at concentrations similar to those in plasma. It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from CELEBREX, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use

Safety and effectiveness in pediatric patients below the age of 18 years have not been evaluated.

Geriatric Use

Of the total number of patients who received CELEBREX in clinical trials, more than 2,100 were 65–74 years of age, while approximately 800 additional patients were 75 years and over. While the incidence of adverse experiences tended to be higher in elderly patients, no substantial differences in safety and effectiveness were observed between these subjects and younger subjects. Other reported clinical experience has not identified differences in response between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

In clinical studies comparing renal function as measured by the GFR, BUN and creatinine, and platelet function as measured by bleeding time and platelet aggregation, the results were not different between elderly and young volunteers.

ADVERSE REACTIONS

Of the CELEBREX treated patients in controlled trials, approximately 4,250 were patients with OA, approximately 2,100 were patients with RA, and approximately 1,050 were patients with post-surgical pain. More than 8,500 patients have received a total daily dose of CELEBREX of 200 mg (100 mg BID or 200 mg QD) or more, including more than 400 treated at 800 mg (400 mg BID). Approximately 3,900 patients have received CELEBREX at these doses for 6 months or more; approximately 2,300 of these have received it for 1 year or more and 124 of these have received it for 2 years or more.

Adverse events from controlled trials: Table 4 lists all adverse events, regardless of causality, occurring in ≥2% of patients receiving CELEBREX from 12 controlled studies conducted in patients with OA or RA that included a placebo and/or a positive control group.

Table 4

Adverse Events Occurring in ≥2% of Celebrex Patients

	Celebrex 400–[illegible] mg/day = 200 mg BID (N=[illegible])	Placebo (N=[illegible])	Naproxen 500 mg BID (N=1366)	Ibuprofen 800 mg TID (N=357)	Diclofenac 75 mg BID (N=[illegible])
Gastrointestinal					
Abdominal pain	4.1%	2.8%	7.7%	9.0%	9.0%
Diarrhea	5.6%	3.8%	6.3%	9.2%	5.9%
Dyspepsia	8.9%	6.2%	12.2%	10.9%	12.8%
Flatulence	2.2%	1.0%	3.6%	4.1%	2.5%
Nausea	3.5%	4.2%	6.0%	3.4%	6.7%
Body as a whole					
Back pain	2.8%	2.8%	2.2%	2.6%	0.9%
Peripheral edema	2.1%	1.1%	2.1%	1.0%	3.5%
Injury-accidental	2.9%	2.3%	3.0%	2.6%	3.2%
Central and peripheral nervous system					
Dizziness	2.0%	1.7%	2.8%	1.7%	2.3%
Headache	15.8%	20.2%	14.5%	16.5%	16.4%
Psychiatric					
Insomnia	2.3%	2.3%	2.8%	1.7%	1.4%
Respiratory					
Pharyngitis	2.3%	1.1%	1.7%	1.6%	2.6%
Rhinitis	2.0%	1.7%	2.4%	2.3%	0.8%
Sinusitis	5.0%	4.3%	4.8%	5.4%	5.8%
Upper respiratory tract infection	8.1%	6.7%	9.9%	9.8%	9.9%
Skin					
Rash	2.2%	2.1%	2.1%	1.7%	1.2%

In placebo- or active-controlled clinical trials, the discontinuation rate due to adverse events was 7.1% for patients receiving CELEBREX and 6.1% for patients receiving placebo. Among the most common reasons for discontinuation due to adverse events in the CELEBREX treatment groups were dyspepsia and abdominal pain (cited as reasons for discontinuation in 0.8% and 0.7% of CELEBREX patients, respectively). Among patients receiving placebo, 0.6% discontinued due to dyspepsia and 0.6% withdrew due to abdominal pain.

The following adverse events occurred in 0.1–1.9% of patients regardless of causality.

Celebrex
(100–200 mg BID or 200 mg QD)

Gastrointestinal: Constipation, diverticulitis, dysphagia, eructation, esophagitis, gastritis, gastroenteritis, gastroesophageal reflux, hemorrhoids, hiatal hernia, melena, dry mouth, stomatitis, tenesmus, tooth disorder, vomiting

Cardiovascular: Aggravated hypertension, angina pectoris, coronary artery disease, myocardial infarction

General: Allergy aggravated, allergic reaction, asthenia, chest pain, cyst NOS, edema generalized, face edema, fatigue, fever, hot flushes, influenza-like symptoms, pain, peripheral pain

Resistance mechanism disorders: Herpes simplex, herpes zoster, infection bacterial, infection fungal, infection soft tissue, infection viral, moniliasis, moniliasis genital, otitis media

Central, peripheral nervous system: Leg cramps, hypertonia, hypoesthesia, migraine, neuralgia, neuropathy, paresthesia, vertigo

Female reproductive: Breast fibroadenosis, breast neoplasm, breast pain, dysmenorrhea, menstrual disorder, vaginal hemorrhage, vaginitis

Male reproductive: Prostatic disorder

Hearing and vestibular: Deafness, ear abnormality, earache, tinnitus

Heart rate and rhythm: Palpitation, tachycardia

Liver and biliary system: Hepatic function abnormal, SGOT increased, SGPT increased

Metabolic and nutritional: BUN increased, CPK increased, diabetes mellitus, hypercholesterolemia, hyperglycemia, hypokalemia, NPN increase, creatinine increased, alkaline phosphatase increased, weight increase

Musculoskeletal: Arthralgia, arthrosis, bone disorder, fracture accidental, myalgia, neck stiffness, synovitis, tendinitis

Platelets bleeding or clotting: Ecchymosis, epistaxis, thrombocythemia

Psychiatric: Anorexia, anxiety, appetite increased, depression, nervousness, somnolence

Hemic: Anemia

Respiratory: Bronchitis, bronchospasm, bronchospasm aggravated, coughing, dyspnea, laryngitis, pneumonia

Skin and appendages: Alopecia, dermatitis, nail disorder, photosensitivity reaction, pruritus, rash erythematous, rash maculopapular, skin disorder, skin dry, sweating increased, urticaria

Application site disorders: Cellulitis, dermatitis contact, injection site reaction, skin nodule

Special senses: Taste perversion

Urinary system: Albuminuria, cystitis, dysuria, hematuria, micturition frequency, renal calculus, urinary incontinence, urinary tract infection

Vision: Blurred vision, cataract, conjunctivitis, eye pain, glaucoma

Other serious adverse reactions which occur rarely (<0.1%), regardless of causality: The following serious adverse events have occurred rarely in patients taking CELEBREX.

Cardiovascular: Syncope, congestive heart failure, ventricular fibrillation, pulmonary embolism, cerebrovascular accident, peripheral gangrene, thrombophlebitis

Gastrointestinal: Intestinal obstruction, intestinal perforation, gastrointestinal bleeding, colitis with bleeding, esophageal perforation, pancreatitis, cholelithiasis, ileus

Hemic and lymphatic: Thrombocytopenia

Nervous system: Ataxia

Renal: Acute renal failure

General: Sepsis, sudden death

OVERDOSAGE

Symptoms following acute NSAID overdoses are usually limited to lethargy, drowsiness, nausea, vomiting, and epigastric pain, which are generally reversible with supportive care. Gastrointestinal bleeding can occur. Hypertension, acute renal failure, respiratory depression and coma may occur, but are rare. Anaphylactoid reactions have been reported with therapeutic ingestion of NSAIDs, and may occur following an overdose.

Patients should be managed by symptomatic and supportive care following an NSAID overdose. There are no specific antidotes. No information is available regarding the removal of celecoxib by hemodialysis, but based on its high degree of plasma protein binding (>97%) dialysis is unlikely to be useful in overdose. Emesis and/or activated charcoal (60 to 100 g in adults, 1 to 2 g/kg in children) and/or osmotic cathartic may be indicated in patients seen within 4 hours of ingestion with symptoms or following a large overdose. Forced diuresis, alkalinization of urine, hemodialysis, or hemoperfusion may not be useful due to high protein binding.

DOSAGE AND ADMINISTRATION

The lowest dose of CELEBREX should be sought for each patient.

Osteoarthritis: For relief of the signs and symptoms of osteoarthritis the recommended oral dose is 200 mg per day administered as a single dose or as 100 mg twice per day.

Rheumatoid arthritis: For relief of the signs and symptoms of rheumatoid arthritis the recommended oral dose is 100 to 200 mg twice per day.

HOW SUPPLIED

CELEBREX 100-mg capsules are white, reverse printed white on blue band of body and cap with markings of 7767 on the cap and 100 on the body, supplied as:

NDC Number	Size
0025–1520–31	bottle of 100
0025–1520–61	bottle of 500
0025–1520–34	carton of 100 unit dose

CELEBREX 200-mg capsules are white, with reverse printed white on gold band with markings of 7767 on the cap and 200 on the body, supplied as:

NDC Number	Size
0025–1525–31	bottle of 100
0025–1525–61	bottle of 500
0025–1525–34	carton of 100 unit dose

Store at 25°C (77°F); excursions permitted to 15–30°C (59–86°F). [See USP Controlled Room Temperature]

Rx only

-10/*5/99

Mfd. by Searle Ltd.
Caguas PR 00725

Marketed by:
G.D. Searle & Co.
Chicago IL 60680 USA
Pfizer Inc.
New York NY 10017 USA

Address medical inquiries to:
G.D. Searle & Co.
Healthcare Information Services
5200 Old Orchard Rd.
Skokie IL 60077

SEARLE Pfizer

Adverse reactions to sulphonamide and sulphonamide-trimethoprim antimicrobials: clinical syndromes and pathogenesis

—Cribb et al, 1996[1]

Inside...a 2-part review of sulfonamide adverse drug reactions (ADRs)

- Part 1: Clinical manifestations of ADRs
- Part 2: Pathogenesis of ADRs, emphasizing hypersensitivity reactions

OCCURRENCE OF ADRs[1]

Since their introduction as antimicrobial agents in the 1930s, sulfonamides have been regularly associated with a variety of ADRs

Cribb et al discuss 3 types of toxicities:

- *Pharmacologic toxicities*: attributable to the nature of the parent drug or active metabolite
- *Intrinsic toxicities*: dose-dependent ADRs
- *Idiosyncratic toxicities*: unpredictable, usually rare, extremely diverse, and often immune-related (frequently referred to as "drug hypersensitivity reactions" or "drug allergy")

The combination sulfonamide, trimethoprim-sulfamethoxazole (TMP-SMX)—first introduced in the late 1960s—has become a mainstay of pneumonia therapy in AIDS patients

- An unusually high incidence of sulfonamide ADRs in AIDS patients has been one result.
- This high incidence has led to heightened interest in and investigation of the mechanisms of sulfonamide ADRs.

Cribb et al provide an extensive review of the latest thinking on sulfonamide ADRs

- The authors present a metabolic hypothesis for the pathogenesis of these ADRs.
- Their emphasis is on the pathogenesis of idiosyncratic toxicities (drug hypersensitivity or allergy).

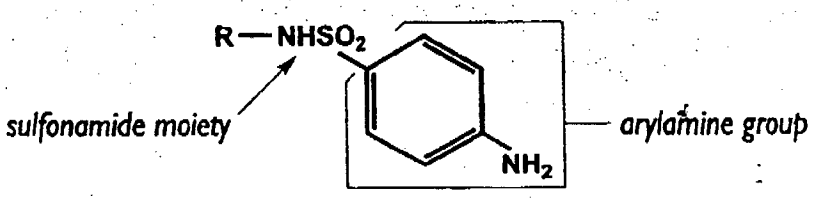
PATHOGENESIS OF ADRs[1]

The critical first step in the pathogenesis of sulfonamide allergenicity is believed to be the formation of hydroxylamine metabolites, the precursors to more reactive metabolites

- Immunological events, however, are also intrinsic to the ultimate pathogenesis of sulfonamide hypersensitivity reactions.
- Drugs alone, due to their low molecular mass, are generally incapable of causing an immune response.
- They need linkage to a macromolecular carrier, usually a protein, to become immunogenic.
- Linkage, in turn, requires the presence of reactive metabolites.

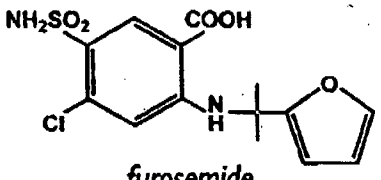
Only *antimicrobial* sulfonamides contain the arylamine group (an aryl ring and an amine structure) that can be bioactivated to a hydroxylamine, the precursor to more reactive metabolites

ANTIMICROBIAL ARYLAMINE

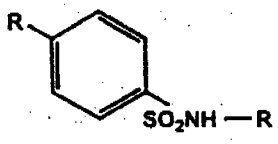


The other sulfonamides, comprising a variety of drug classes and compounds, lack an arylamine group

NON-ARYLAMINES



furosemide



tolbutamide, chlorpropamide

SULFONAMIDE METABOLISM: ALL SULFONAMIDES ARE NOT THE SAME[1]

Based on recent metabolic and immunologic understanding, the long-held belief that cross-allergenicity is common among various sulfonamides may be open to question

- There is, in fact, very little literature describing clinical cross-reactivity between sulfonamide drugs of any class.[1]
- Several patients have been reported to be sensitive to one sulfonamide but not to other sulfonamide-containing drugs.[1]

"...metabolic susceptibility factors for sulphonamide antimicrobials would not be shared by non-arylamine containing sulphonamides. A differing set of metabolic factors would be expected to influence the occurrence of toxicities associated with those compounds and there is no apparent metabolic basis for a shared risk."[1]

Sulfonamides can generally be grouped into 2 categories:

- *Antimicrobial*, arylamine sulfonamides
  - — Bactrim™ (trimethoprim/sulfamethoxazole), Septra® (trimethoprim/sulfamethoxazole), and Gantrisin® (sulfisoxazole)
- *Other*, non-arylamine sulfonamides
  - — Diuretics such as HydroDIURIL® (hydrochlorothiazide) and Lasix® (furosemide)
  - — Antihypertensives/diuretics such as Hyzaar® (losartan/hydrochlorothiazide) and Ziac® (bisoprolol/hydrochlorothiazide)
  - — Sulfonylureas such as Glucotrol® (glipizide), Orinase® (tolbutamide), Amaryl® (glimepiride), and Glynase® PresTab® (micronized glyburide)
  - — Additional medications such as Benemid® (probenecid), Trusopt® (dorzolamide hydrochloride), Imitrex® (sumatriptan), and Flomax® (tamsulosin)

The antimicrobial metabolites may be more likely to cause primary allergic reactions than the metabolites of the "other" sulfonamides

Reference: 1. Cribb AE, Lee BL, Trepanier LA, Spielberg SP. Adverse reactions to sulphonamide and sulphonamide-trimethoprim antimicrobials: clinical syndromes and pathogenesis. *Adverse Drug React Toxicol Rev.* 1996;15:9-50.

COMMONLY AVAILABLE SULFUR-CONTAINING DRUGS*

Sulfur-containing drugs—Non-sulfonamides

- Amoxil® (amoxicillin)
- Captopril generic
- Prilosec® (omeprazole)
- Zantac® (ranitidine)
- Vioxx® (rofecoxib)
- Clinoril® (sulindac)
- Dapsone generic

Sulfur-containing drugs—Sulfonamides

Arylamines

Antimicrobials "Sulfa Drugs"

- Bactrim® (trimethoprim/sulfamethoxazole)
- Septra® (trimethoprim/sulfamethoxazole)
- Gantrisin® (sulfisoxazole)
- Sultrin® (sulfachizole/sulfacetamide/sulfabenzamide)
- Novacet® (sodium sulfacetamide 10% and sulfur 5%)
- Pediazole® (erythromycin ethylsuccinate and sulfisoxazole acetyl for oral suspension)

Non-arylamines

Diuretics/ Combination diuretics

- HydroDIURIL® (hydrochlorothiazide)
- Lasix® (furosemide)
- Capozide® (captopril/hydrochlorothiazide)
- Diuril® (chlorothiazide)
- Dyazide® (hydrochlorothiazide/triamterene)
- Hyzaar® (losartan/hydrochlorothiazide)
- Lozol® (indapamide)
- Maxzide® (triamterene/hydrochlorothiazide)
- Tenoretic® (atenolol/chlorthalidone)
- Vaseretic® (enalapril maleate/hydrochlorothiazide)
- Zestoretic® (lisinopril/hydrochlorothiazide)
- Ziac® (bisoprolol/hydrochlorothiazide)

Sulfonylureas

- Diabeta® (glyburide)
- Glynase® PresTab® (micronized glyburide)
- Orinase® (tolbutamide)
- Amaryl® (glimepiride)
- Glucotrol® (glipizide)
- Diabinese® (chlorpropamide)

Other

- Celebrex® (celecoxib capsules)
- Benemid® (probenecid)
- Trusopt® (dorzolamide hydrochloride)
- Flomax® (tamsulosin)
- Imitrex® (sumatriptan)

* This chart is not a complete list of all sulfur-containing drugs. Rather, it is illustrative of the wide variety of commonly available sulfur-containing medications representing many therapeutic classes.

- Consult complete prescribing information for indications, contraindications, warnings, precautions, and adverse reactions.

TAB 23

Guidance for Industry
Clinical Studies Section of Labeling for Prescription Drugs and Biologics-- Content and Format

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

Comments and suggestions regarding this draft document should be submitted within 90 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit comments to Dockets Management Branch (HFA-305), Food and Drug Administration, 12420 Parklawn Dr., rm. 1-23, Rockville, MD 20857. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions regarding the content of this draft document, contact (CDER) Janet Jones, 301-594-6758 or (CBER) Toni Stifano, 301-827-6190.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)
July 2001

Labeling

Copies of this Guidance are available from:

Office of Training and Communications
Division of Drug Information, HFD-240
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane, Rockville, MD 20857
(Phone 301-827-4573)
Internet: http://www.fda.gov/cder/guidance/index.htm.

or

Office of Communication, Training and
Manufacturers Assistance, HFM-40
Center for Biologics Evaluation and Research
Food and Drug Administration
1401 Rockville Pike, Rockville, MD 20852-1448
Internet: http://www.fda.gov/cber/guidelines.htm.
Fax: 1-888-CBERFAX or 301-827-3844
Mail: the Voice Information System at 800-835-4709 or 301-827-1800.

Labeling

TABLE OF CONTENTS

Guidance for Industry[1]

Clinical Studies Section of Labeling for Prescription Drugs

and Biologics--Content and Format

This draft guidance, when finalized, will represent the Food and Drug Administration's (FDA's) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. An alternative approach may be used if such approach satisfies the requirements of the applicable statutes and regulations.

I. INTRODUCTION

This guidance is intended to help applicants decide (1) what studies should be included in the CLINICAL STUDIES section of medical product labeling, (2) how t describe individual studies, and (3) how to present study data, including presentation of data in graphs and tables. This guidance is intended to make the CLINICAL STUDIES section of labeling more useful to prescribers and to promote consistency in the content and format of the section across drug product classes and within drug classes and indications. This guidance also calls attention to the advertising and promotional implications of data and statements contained in the CLINICAL STUDIES section.

The overriding objective in labeling is to provide the information that is most useful to prescribers in treating their patients. In some cases, making the information in the CLINICAL STUDIES section of labeling more useful to prescribers could warrant significant departures from past labeling practices.

II. IDENTIFYING STUDIES FOR INCLUSION IN THE CLINICAL STUDIE SECTION

The CLINICAL STUDIES section of product labeling should provide a concise, accurate summary of the evidence supporting effectiveness - generally, the adequate and well-controlled

studies[2] that address effectiveness of the drug or biologic[3] for its approved indicatior This section of the labeling is not intended to describe all available efficacy[4] data. Redundant information should be omitted or described briefly without detail. If there are multiple studies that address the same effectiveness issue, the subset selected for presentation should ordinarily reflect the overall conclusions derived from the application database as a whole (e.g., should not suggest a larger treatment effect tha the database as a whole). However, study results that are inconsistent with the overal conclusions (e.g., absence of a treatment effect) should be included when they provide important information about drug effectiveness that is not otherwise availabl (e.g., information about a population subset, dose response, or the limitations of effectiveness).

A. Studies That Should Usually Be Included in the Clinical Studies Section

The following are the types of studies that should usually be included in the CLINICAL STUDIES section:

- Clinical studies that provide primary support for effectiveness.

- Clinical studies that provide important information about the limitation of effectiveness.

- Other clinical studies that contribute important efficacy data not provided by those trials that provide primary support for effectiveness (e.g., information about a population subset, dose, dose-response, effect size).

B. Studies That Should Usually *Not* Be Included in the Clinical Studies Section

The following are the types of studies that should usually not be included in th CLINICAL STUDIES section, unless they also meet one of the factors in II.A (above):

· Clinical studies with results that imply effectiveness for an unapproved indication.

· Active control clinical studies that imply comparative efficacy or safety claims not supported by substantial evidence.

· Studies that are not adequate and well-controlled. For any exceptions, the limitations of the study and the compelling reasons for inclusion should be stated.

III. DESCRIBING STUDIES IN THE CLINICAL STUDIES SECTION

A. General Principles

1. Focus on Efficacy Data

The primary objective of the CLINICAL STUDIES section is to summarize (1) the evidence supporting effectiveness in the patients who were studied, (2) the critical design aspects of the studies, including the populations studied and endpoints measured, and (3) the important limitations of the available evidence. Ordinarily, safety data should be described in the ADVERSE REACTIONS section. However, in unusual cases it may be more clear or concise to present critical safety data in the CLINICAL STUDIES section, along with the study description and the efficacy data (e.g., when there is a study designed to evaluate a specific safety endpoint). If safety data are presented in the CLINICAL STUDIES section, they should be cross-referenced in the ADVERSE REACTIONS section and other sections, as appropriate.

2. Amount of Detail

In general, the amount of detail needed to provide a useful description o a study will depend on the indication, the trial design, the familiarity of the drug or drug class, and the extent to which the information adds to a understanding of the clinical effects of the drug and how the drug should be used.

Ordinarily, more detail is needed in the following situations:

· The study responses measured are of critical health importance. Typically, such responses would be direct measures of a meaningful clinical outcome (e.g., mortality, stroke or acute myocardial infarction rates, fracture rates) but could also include

effects on important surrogate endpoints (e.g., cholesterol or hemoglobin A1C).

· The study results represent a significant advance in the treatment of a disease or condition or provide important information about a drug's activities relative to the drug's therapeutic class.

· The study enrolled a very specific population and the results may not be applicable to other populations.

· The study results are not typical of what would be expected for that drug class and indication. For example, the study results demonstrate a particularly marginal response or a response for which the clinical meaning or implications are unclear.

· The study results demonstrate that a new agent offers a clear advantage over existing therapy (see section III.A.4 below for discussion of comparative claims).

· The study uses an unfamiliar endpoint (e.g., a novel surrogate endpoint), or there are important limitations and uncertainties associated with an endpoint.

Ordinarily, less detail is needed in the following situations:

· The new drug appears to have effects that are typical of its class.

· The clinical endpoints measured in the study are not readily measurable or applicable in clinical practice (e.g., exercise testing in a study of heart failure can demonstrate effectiveness but does not translate to a measurable clinical outcome).

In these cases, it could be useful to describe the study in general terms (e.g., population, duration, measurements, and qualitative outcome) without providing detailed results.

3. Endpoints

The CLINICAL STUDIES section should present those endpoints that are essential to establishing the effectiveness of the drug (or that show the limitations of effectiveness) and those that provide additional useful and valid information about the activities of the drug. Endpoints presented should be endpoints the Agency has accepted as evidence of effectiveness, or closely related endpoints that may be more easily understood by clinicians. When it would be informative, the CLINICAL STUDIES section can also discuss other endpoints that were shown to be affected by the drug and endpoints that would have been expected to be influenced by the drug, but were not.

· **Composite Endpoints:** In general, effects on all components of composite endpoint should be presented. Presentation of all components reveals which components are driving the result and which components may be unaffected, or even adversely affected, by treatment with the drug. When there is a range of effects on the components of a composite endpoint, selectively presenting only a single component of the composite endpoint, or presenting only the change in the composite endpoint, can be misleading.

· **Primary and Secondary Endpoints:** The terms *primary endpoint* and *secondary endpoint* should only be used when they would be helpful to understanding a drug's effect.

· **Closely Related Endpoints:** If two or more endpoints are closely related and convey essentially the same information, only one should be presented.

4. Comparative Data

Comparative data should generally not be included in labeling unless the data are from adequate and well-controlled studies that can support a comparative claim. If, however, the results from an active comparator arm and identity of the active comparator contribute information that is essential to a clinician's understanding of the drug's effects, the results and identity should be included in labeling. In such cases, the labeling should make clear that no comparative claim has been established and should disclose any limitations of the comparative data (e.g., if the comparator was administered in a suboptimal or unapproved regimen).

For example, when describing a clinical trial with three treatment arms (study drug, active control, and placebo) in which the comparison of study drug to placebo yields important efficacy information, the name of the active control and the results from that arm should be omitted if those data are not adequate to support a comparative claim. In contrast, when an active control, non-inferiority trial is critical to establishing effectiveness of a new drug, the name of the control and the results from the control arm should be included even though the data do not support a comparative claim. The labeling should indicate that the data do not support a comparative claim and should disclose any other limitations of the data.

B. Describing the Study Design

Usually, the description of the study design should include the following:

1. Major Design Characteristics

The major design characteristics should be identified, including level of

blinding (e.g., double-blinded, partially blinded, open-label), type of controls (e.g., placebo, active, historical), duration of the study, method of allocation to treatment groups (e.g., randomization), and use of a run-in period to identify potential responders or eliminate placebo responder from subsequent phases of the study. Often these factors can be summarized in a phrase such as "randomized, double-blind, placebo-controlled study."

2. Treatment Arms

The dose, regimens, and any titration procedure should be identified for each trial arm.

3. Concomitant Therapy

Information about concomitant therapies should be included to the exten it is important to understanding the use of the study drug or its effects.

4. Study Population

The description of the study population should identify those characteristics of the population that are important to understanding how to interpret and apply the study results. The description should identify important inclusion and exclusion criteria, demographic characteristics, baseline values of any clinically relevant variables that would be important to understanding the treatment effect, and other characteristics of the population that have implications for the extent to which results can be generalized. For example, the description should discuss enrollment factors that exclude patients prone to adverse effects, the age range of the study population, a baseline value that results in a study population that is more or less sick than usual, or a study population enriched by a study design that eliminates nonresponders.

5. Critical Endpoints

Endpoints critical to establishing efficacy should be identified, and those that are not commonly understood should be defined.

C. Summarizing Study Findings

When a detailed summary of study findings is important to understanding the clinical effects of the drug (see section III.A.2 for a discussion of when more detail is important), the following elements should be addressed:

1. Disposition of Patients

Ordinarily the discussion of disposition of patients should include the following:

· The number of patients enrolled.

· The number of subjects completing the study.

· The number of patients discontinuing the study and reasons for discontinuation.

· For a study with a run-in period or other distinct phases, the number of patients entering each phase and the number of patients not progressing to the next phase (can be very important for understanding the study results).

2. Treatment Effect[5]

The summary of findings should describe the clinical outcome of the treatment relative to comparator (e.g., placebo or active).

· **Absolute vs. Relative Difference:** When presenting differences between study group and comparator, it is important to present the absolute difference between treatment groups for the endpoint measured, not only the relative difference. For example, if mortality is 6% in one study arm and 8% in the other, the absolute difference (2%) should be presented.

· **Group Results and Individual Patient Data:** Typically, the treatment effect is presented as a mean or median result accompanied by a measure of uncertainty or distribution of results for the treated groups. However, providing individual patient data for all treatment groups can be a useful alternative for describing the clinical effect of a drug. This can be done by including a graphical presentation of the distribution or cumulative distributio of responses among individual patients (see appendix for example of graphical methods for presenting individual patient data).

· **Combined Data:** In certain situations, analyses of data combine from multiple efficacy studies can be useful for estimating the treatment effect. These analyses should be included only when they are scientifically appropriate and useful to better characterize the treatment effect. Meta-analytic graphs (see appendix) can be useful for displaying confidence intervals from several studies.

· **Uncertainty of Treatment Effect:** A confidence interval is typically more informative than a p-value and is the preferred method for describing uncertainty of the treatment effect. Although both a confidence interval and a p-value provide information about the uncertainty of the treatment effect, the confidence interval also provides information about the likely size of the treatment effect. A p-value can be included with a confidence interval, but should not be used alone, as it is potentially misleading.

3. Describing Results Within Treatment Groups

Because the comparison between treatment groups is critical to an understanding of the treatment effect, results for both the study drug and comparator should be presented. There is almost never a reason to show only results from the study drug group. This is especially important for studies with large effects in the placebo group, where presentation of results uncorrected for the placebo group

response can be highly misleading. When results from active control arms are

discussed, caution should be taken to avoid the implication of an unsubstantiated

comparative claim (see section III.A.4). The presentation of results within a treatment group should include, where appropriate, information about the variability of individual patient responses within the treatment group. This can be accomplished with, for example, standard deviations or box plots (see appendix for examples of graphical methods for presenting results within treatment groups).

4. Demographic Subgroups

The CLINICAL STUDIES section should include a summary statement about the results of required explorations of treatment effects in age, gender, and racial subgroups (21 CFR 314.50). Compelling results from analyses of other subgroups of established interest should also be presented, with a caution statement, where appropriate, about the inherent risks of unplanned subgroup analyses. The summary statement should report the findings of analyses that had a reasonable ability to detect subgroup differences and should note when analyses were not useful because of inadequate sample size. Examples of appropriate summary statements include:

- The database was not large enough to assess whether there were differences in effects in age, gender, or race subgroups.

- Examination of age and gender subgroups did not identify differences in response to (study drug) among these subgroups. There were too few black patients to adequately assess differences in effects in that population.

- Examination of age and gender subgroups suggested a larger treatment effect in women (possibly resulting from the larger mg/kg dose in women), but no age-related differences. There were too few black patients to adequately assess differences in effects in that population.

D. Presenting Data for Different Types of Outcomes

Data on outcomes of treatment should be presented only if the outcome is of clinical significance.

1. Categorical Outcomes (e.g., success or failure)

For categorical outcomes, the number (or percentage) of outcomes for al randomized patients should be shown. For example, the total sample siz for the treatment group, the number of successes, the number of failures. and the number of unknown status should be given. Where informative, those patients whose outcome status is unknown can be further differentiated by including the number who dropped out due to adverse events, the number who were lost to follow-up, or any other pertinent distinction. If only percentages are reported, the denominator should be included.

2. Continuous Variables

For continuous variables, means or medians, accompanied by the standard deviation, are the usual methods for presenting data. When means or medians are used, the magnitude of variability in patient responses should be discussed, and the number of subjects remaining on study at each time point should be given. When means or medians do no adequately convey the variability of responses, it might be useful to display individual responses (e.g., by graphical representation of the cumulative distribution of responses - see appendix). It is important to include the baseline value when reporting any change (either numerical or percent change) from that baseline.

3. Time-to-Event Endpoints

When time-to-event endpoints (e.g., mortality) are used, median or mear survival alone is not usually an adequate descriptor. Survival curves (or event-free survival curves) and hazard ratios are often effective ways to display such data. Data can also be summarized at specific times (e.g., prevalence at 3, 6, 9, 12 months) or at specific event frequency (e.g., time to 25%, 50%, and 75% prevalence of events). The number of patients evaluated at a given interval or frequency should be specified.

4. Graphs or Tables

Ordinarily a graph or table is more effective than text alone in communicating study results, and one or the other should be used when presenting study results in the CLINICAL STUDIES section. See the appendix for guidance on the use of graphs and tables in the CLINICAL

STUDIES section of labeling.

E. Advertising and Promotional Considerations

Advertising and promotional materials make frequent use of statements or data appearing in the CLINICAL STUDIES section. Therefore, the CLINICAL STUDIES section should be carefully scrutinized to ensure that its content does not suggest or imply claims for indications, doses, regimens, or comparative effectiveness that are not adequately supported. Words or phrases that lack a commonly understood meaning (e.g., imprecise quantitative terms), are not easily defined, are vague, are misleading, or are promotional in tone should be avoided. Examples include large or small (instead use actual size or amount), well-conducted (instead provide specifics about the study design), extensively studied (instead provide specifics about the database), rapid (instead specify change/unit time), trend (instead provide specifics about the outcome), potent (instead give the size of the effect), pivotal study (instead describe as major efficacy study), and highly significant (instead provide the confidence interval

F. Updating the Clinical Studies Section

The CLINICAL STUDIES section should be updated when new, important information becomes available. Outdated information should be promptly revised or replaced.

APPENDIX

Presenting Study Results in Tables and Graphs

I. INTRODUCTION

This appendix provides guidance on the use of graphs and tables in the CLINICAL STUDIES section of labeling. When clinical data are to be presented in some detail, ordinarily tables and graphs are better than text alone because they convey the desire information more effectively. The following general principles apply to the use of tables and graphs:

· Tables and graphs should depict study results clearly, fairly, and accurately.

· Text accompanying a table or graph should avoid needless repetition of information that would be clear from viewing the table or graph. The text should serve as an aid to interpreting the most important data presented in the table or graph. Often the statement, "Results are found in Table X," is sufficient.

· Tables and graphs should be next to the text that mentions the table or graph, and that text should refer to the table or graph. Small tables can be embedded in the text.

· Tables and graphs should have clear titles and clearly labeled axes to limit the need to use text to explain what is portrayed.

II. GRAPHS

A. Use of Graphs

· To present a large amount of data, such as individual patient data points (cumulative responses).

· To illustrate changes over time.

· To illustrate differences in magnitude of response, particularly where more than two treatment groups are being compared.

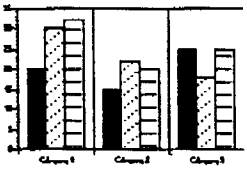
· To convey dose-response information.

B. Graphs Most Commonly Used in the Description of Clinical Trial Efficacy Data

Histogram

Illustrates individual patient data by presenting the number or percentage of patients (y-axis) exhibiting a given response (x-axis) over the whole response range.

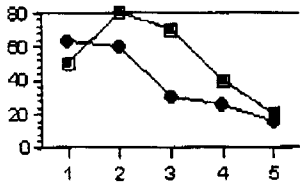
Bar Graph



(1) Compares subgroups where each bar represents a subgroup within a treatment arm, and the length of the bar represents the group response for the outcome variable, (2) shows the percentage or frequency of patients (the y-axis) exhibiting a categorical response, and (3) displays the principal results of several similar trials. In most cases, it is helpful to include error bars. A bar graph should not be used to illustrate just a few numbers that could be summarized better in a table. 3-D graphs should be avoided because they make comparisons between bars very difficult. Stippling or other small patterns in bars should also be avoided because they can be difficult to see after reduction

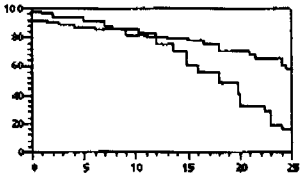
or reproduction.

Line Graph



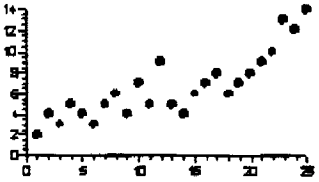
Most often illustrates responses (y-axis) over time (x-axis). It is helpful in many cases to include error bars and number of patients remaining on study treatment at each time point. Similar graphs can be used to show dose response with response on the y-axis and dose on the x-axis.

Survival Curve



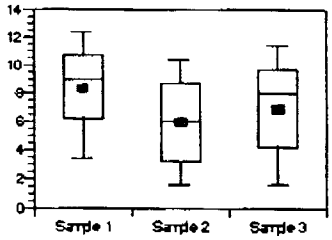
Depicts time-to-event data for events like death or recurrence of disease. Usually, Kaplan-Meier estimates of the proportion of patients surviving are plotted, but some plots show the raw cumulative incidence rates over time.

Scatter Plot



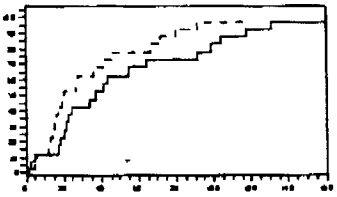
Shows the relationship between two (usually continuous) variables for individual patients, such as response (y-axis) related to blood levels or some other measure (x-axis).

Boxplot



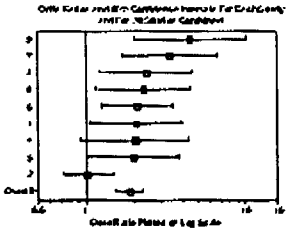
Illustrates the distribution of data for a single group. Several plots in a single graph are useful for comparing distributions. Boxes represent the range of values from the 25th percentile to the 75th percentile. The definition for the length of the whiskers (lines extending out from each end of the box) varies with software packages and should be defined with the plot (e.g., the ends represent the 10th and 90th percentile, the minimum and the maximum, or lower adjacent value computed as 1.5 times the interquartile range minus the 25th percentile and the upper adjacent value computed as 1.5 times the interquartile range plus the 75th percentile).

Cumulative Distribution Plot



Depicts individual patient data. The y-axis represents a cumulative percentage of subjects with a response at least as large as the effect shown on the x-axis. These distributions can be graphed using bars or using a step graph. A cumulative distribution plot could call for additional text that describes how to read the graph. For example, the following text could be helpful: "A curve shifted to the left represents a more effective treatment. A response of at least *x* was seen by *a percent* of the patients on New Drug and *b percent* of the patients on Placebo."

Meta-analytic Graph



Depicts summary estimates (usually a treatment difference) for several studies (or centers) on one graph. It is useful for illustrating a lack of consistency across studies. Ordering the responses by magnitude enhances the visualization of the effects. Similar displays can show results in demographic or other subsets (e.g., disease severity, background therapy).

C. Features of a Good Graph

· **Title:** The following information should be included in the title: the

name of the study, the type of data, the timepoint, and important features of the patient population (e.g., Intent-to-Treat, Evaluable, age range if relevant). For ease of reading, the beginning of each word should be capitalized, not every letter in the title.

· **Axis Label/Title:** Ordinarily each axis should be labeled. Units of measurement should be included.

· **Ticks and Grids:** Ticks for each axis should be labeled so that the reader does not have to interpolate to understand the data. A graph will appear less cluttered if ticks face away from the graph and if grids are eliminated.

· **Axis Scale:** The treatment effect should not be exaggerated (e.g., interruptions) by the scale of measurement (generally the y-axis), but the scale of measurement should show the scale of the efficacy variable. The scales should be consistent for like graphs within the label. Differences in scales among labels of drugs in the same class should be avoided if possible, as they can lead to misleading comparisons.

· **Symbols:** Symbols should be easily distinguishable by size, shape, or fill (e.g., open symbols for placebo and closed symbols for treatment).

· **Footnotes:** A footnote should be used if further information would be helpful to explain the content of the graph (e.g., the meaning of a term used, the meaning of a symbol). Ordinarily, statements interpreting the graph should be included in the text accompanying the graph and not in footnote.

· **Error Bars:** It should be clear from the graph which measure of variability is used to define the error bars (standard deviation, standard error, percentiles).

· **Font Size:** To ensure the graph is readable, careful thought should be given to selecting the font size for labels and symbols. Graphs in labelin and in the *Physicians Desk Reference* (PDR) are often reduced in size to about 60 mm by 50 mm.

· **Legend:** The graph should not be overpowered by the legend. Labels directly on the graph are preferable to a legend.

· **Sample Size:** Including sample sizes for each group often helps the reader interpret the graph. Sample sizes can be identified in text within the graph or in a small table just below the graph.

· **Uncertainty of Treatment Effect:** Differences should be accompanied by the appropriate measure of uncertainty (confidence interval or p-value). Differences that are not statistically significant should be identified as such.

III. TABLES

A. Use of Tables

· To present simple, descriptive statistics such as medians, means, standard deviations, and sample size for both treatment groups or for only a few time points.

· To summarize data from more than one efficacy variable.

· To present exact values if that information is desirable.

B. Features of a Good Table

· **Title:** The following information should be included in the title: the name of the study, the type of data, the timepoint, and the patient population (Intent-to-Treat, Evaluable). For ease of reading, the beginning of each word should be capitalized, not every letter in the title

· **Units:** The units of measurement for the data presented should be included in the table, either in the title or column headings. When presenting percentages, it is helpful to include the percent sign, particularly when several numbers are included on one line (such as mean percentages and sample sizes). Only include the number of digits after the decimal that are significant or meaningful.

· **Sample Size:** The sample size for each treatment group should be included in the table. Also, the age range should be identified when relevant.

· **Baseline Data:** Baseline data should be included whenever applicable.

1 This guidance has been prepared by the Medical Policy Coordinating Committees in the Center for Drug Evaluation and Research (CDER) and the Center for Biologic Evaluation and Research (CBER) at the Food and Drug Administration.

2 See 21 CFR 201.57(m).

3. This guidance applies to drug and biological products. For the purposes of this guidance, the term *drug* will be used to include both drug and biological products.

4 As used in this guidance, the term *efficacy* refers to the findings in an adequate and well controlled clinical trial, and the term *effectiveness* refers to the regulatory determination that is made on the basis of clinical efficacy and other data.

5 *Treatment effect* means the effect that can be attributed to the drug. It is typically derived from a comparison of two prospectively identified treatment arms. Examples of such comparisons include differences in proportions, differences in means, or hazard ratios.

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